NATAP

NATIONAL
AIDS TREATMENT
ADVOCACY PROJECT

Hepatitis C and HCV/HIV Co-infection Treatment and Policy

The most current paper on treatment and policy for Hepatitis C and Co-infection

This comprehensive report covers many of the current issues and questions surrounding Hepatitis C and HCV/HIV Co-infection. It addresses topics such as: transmission, testing, treatment, management of side effects, outcomes of therapy, new treatments, and many other important topics such as treatment access, cost and 12-week stopping rule.

National Institute of Diabetes & Digestive & Kidney Diseases of the NIH (NIDDK).
Prepared by Jules Levin, NATAP

--Natural course of history of disease progression in HCV and HCV/HIV co-infection

--Transmission of HCV

--Testing: genotype, viral load, genotype, stopping therapy at week 12 or 24

--Diagnostic tests: understanding the biopsy, ALT

--Treatment for HCV in mono- and coinfected patients

--Early viral response rule: stopping therapy at week 12 or 24

--How does HAART affect the liver and what you can do about it

--Management of side effects and adverse events, and tolerability of therapy

--Who should be treated: HIV, IVDUs

--Retreatment with pegylated interferon plus ribavirin for previously treated patients

--Outcomes of therapy

--Maintenance therapy

--New treatments in early development

--Treatment access and comparison of costs

--HCV/HIV co-infection policy and research direction and implications

--Research findings for liver transplantation in HIV-infected patients

The hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the United States. It accounts for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. About 4 million Americans, or 1.8 percent of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. 2.7 million have chronic Hep C. Hepatitis C causes an estimated 8,000 to 10,000 deaths annually in the United States. At the NIH HCV Consensus Conference in June 2002 HCV was called an epidemic.

African-Americans and Hispanics are disproportionately affected. The rate of HCV-infection among IVDUs is very high and IVDUs are the largest group of people infected with HCV. Among HIV-infected individuals 30% have HCV but among those infected with HIV by IVDU 60-90% are estimated to have HCV, totaling about 300,000 with co-infection in the USA. Several studies suggest that HIV accelerates HCV progression at least 2-fold. HCV is the most prevalent blood-borne disease in the USA. 18% in an outpatient VA clinic had HCV in a study of 1000 persons. Among homeless vets the rate in a study was 40%. 39% had HCV in a prison study in California, and it was 55% among young women. The majority of people who die of HCV are 44-54 years of age.

A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease. At least 75 percent of patients with acute hepatitis C ultimately develop chronic infection, and most of these patients have accompanying chronic liver disease.

Chronic hepatitis C varies greatly in its course and outcome. Chronic hepatitis C can cause cirrhosis, liver failure, and liver cancer. At one end of the spectrum are patients who have no signs or symptoms of liver disease and completely normal levels of serum liver enzymes. Liver biopsy usually shows some degree of chronic hepatitis, but the degree of injury is usually mild, and the overall prognosis may be good. At the other end of the spectrum are patients with severe hepatitis C who have symptoms, HCV RNA in serum, and elevated serum liver enzymes, and who ultimately develop cirrhosis and end-stage liver disease. In the middle of the spectrum are many patients who have few or no symptoms, mild to moderate elevations in liver enzymes, and an uncertain prognosis. These patients may go onto develop cirrhosis after 30, 40, or 50 years. Researchers estimate that at least 20 percent of patients with chronic hepatitis C develop cirrhosis, a process that takes 10 to 20 years or longer. After 20 to 40 years, a smaller percentage of patients with chronic disease develop liver cancer.

Some researchers estimate that about 20 percent of patients develop cirrhosis within 10 to 20 years of the onset of infection. 30-

40% will never develop cirrhosis. About 40% may develop cirrhosis after 30, 40, or 60 years. Other researchers, including the NIH have reported that estimates of the proportion of chronically infected persons who develop cirrhosis 20 years after initial infection have been substantially higher from retrospective studies (17 to 55 percent) than from prospective studies (7-16 percent). The actual risk of progressive disease at 20 years is now considered to be closer to the estimates from prospective studies.

Cirrhosis can lead to liver cancer (hepatocellular carcinoma, HCC) and end stage liver disease or death. Liver failure from chronic hepatitis C is one of the most common reasons for liver transplants in the United States. Hepatitis C is the cause of about half of cases of primary liver cancer in the developed world. Men, alcoholics, patients with cirrhosis, people over age 40, and those infected for 20 to 40 years are more likely to develop HCV-related liver cancer.

HIV Co-infection

Results from a number of studies show that HIV accelerates HCV progression. The various results show an increased acceleration of 2-6 times. This suggests that HIV-infected patients may develop cirrhosis more quickly; and liver cancer and end stage liver disease more quickly. We have not had very many studies to clearly define if HCV progresses more quickly in HIV, nor have we had any studies to define the rate of progression of HCV in HIV-infected patients. This makes it difficult to provide estimates of what percentage of patients will progress to cirrhosis, as we can do with HCV monoinfected patients, and how many years this will take. At this point most doctors appear to accept that HIV accelerates HCV progression and feel it's crucial to consider this in deciding when to begin HCV therapy. Doctors are very concerned about deferring HCV therapy in the HIV-infected patient who has fibrosis with stage 2 disease. If a patient defers therapy close monitoring can be crucial. Some doctors recommend starting treatment in coinfected patients at stage 2 and may suggest considering treatment in stage 1.

There is a concern about how HAART medications may affect a patient's liver disease. The HIV antiretroviral drugs pass through the liver and liver enzymes (ALT) can be elevated mildly or more severely in a minority of cases. Having HCV or elevated ALT before starting HAART increases the risk that liver enzymes will be elevated. Although all the HIV drugs can be associated with ALT elevations, some drugs or combinations may be more prone to cause this. All the HIV drugs have an affect on the liver. It may be helpful to select a regimen, if possible, that is less likely to cause ALT elevations.

The real question is what is the potential for harm to the liver from HAART medications for the person with HCV or HBV, or to the HIV+ person without hepatitis. Some patients are unwilling to start HIV therapy due to this concern, and some patients are nervous about staying on HIV therapy due to this concern and if they see ALT elevations while on HIV therapy. Some patients stop their HIV therapy due to this without telling their doctor.

There are some other factors affecting HCV+ patients associated with taking HIV medications. Some HAART medications, such as a PI or double or boosted PI regimen, may cause elevated fats in the blood. These fats may get deposited in the liver; this is called fatty liver but has not been studied in HIV-infected patients. NRTIs may cause mitochondrial toxicity which can damage cells and occur in the liver cells. Such toxicity may not necessarily cause severe damage to the cells. But bear in mind, Ribavirin is an NRTI. A small number of HIV-infected patients from a study who were taking d4T/ddI and then added ribavirin and interferon developed pancreatitis and hyperlactatemia. HCV and HIV infected patients can get increased glucose and diabetes. Patients with HIV experience higher rates of diabetes and it can be associated with certain protease inhibitors. Patients with HCV are more likely to have diabetes then people without HCV. A damaged liver may be a factor in reduced or altered capacity to process fats and sugar. Two small studies find that patients with HCV/HIV may be more likely than HIV-infected patients to develop insulin resistance and diabetes. Patients with HIV are more likely to experience bone loss, reduced bone mineral density than people without HIV. Osteopenia and osteoporosis are more common in people with HIV than in people without HIV. A bone fracture can result from bone disease. HCV is associated with bone loss. This means people infected with HCV are more likely to have reduced bone mineral density than people without HCV. Study found HCV/HIV coinfected patients may be more likely to develop lipodystrophy than HIV-infected. Lipodystrophy is the term to describe body changes that are observed in a percentage of patients with HIV, often developing on HIV treatment. The physical manifestation includes fat loss in the face, rear end, or periphery, and/or fat accumulation in the belly and in the breasts more often for women. After initiating interferon plus ribavirin therapy for HCV weight loss may become more exaggerated in HIV-infected individuals, and this may be associated with fat loss in the periphery.

So what can you do about this?

Not treating HIV can have severe consequences, since HIV can progress more quickly than HCV. Deferring HIV therapy when the timing is appropriate for a patient can be risky, HIV can seriously progress -- CD4 counts can go down, and infections can develop. If a patient has <200 CD4s it is important to try to raise the Cd4 count with HIV therapy. But if you haven't yet been treated for HIV it may be beneficial to consider HCV treatment first. This depends on your personal situation (CD4s, HIV viral load), but improving the condition of the liver may make HAART more tolerable. Selecting a HAART regimen that may be the least harmful to the liver may be helpful.

There has been little well done research on how HIV drugs affect the liver in the HCV+ patient. One French study found patients

on HAART containing a PI did not see fast HCV progression. The same theory might apply to any HAART regimen that reduces viral load & increases CD4s. But this study was poorly conducted, has not been adequately confirmed with additional studies, and many doctors and researchers are skeptical of this theory. Other small studies have found that HAART drugs may affect the liver in a negative way. But all drugs affect the liver. The real question is do the HAART drugs have a significant negative clinical impact on HCV disease progression? We don't have an answer to this question yet. This is somewhat of a controversial issue. Doctors and researchers have different opinions. A number of researchers do not feel that HAART damages the liver in HCV-infected patients to a significant degree, while other doctors are unsure. But, there have no definitive studies to date in HIV-infected individuals on HAART evaluating the effect of antiretroviral HIV drugs on liver disease in HCV or HBV infected patients.

One way to address these concerns is to consider starting HCV therapy before HAART, shortly after starting HAART, and in the early stages of HCV disease.

Transmission of HCV

Previous to 1991-1992 transfusion was a leading cause of HCV transmission. But at that time a blood screening test was instituted and the risk of transmission by transfusion has been very low since then. The main route of transmission for HCV today is by IVDU. HCV is transmitted by blood-to-blood contact, as is HIV. Most new HCV infections occur now from IVDU by sharing a contaminated needle or by sharing the paraphernalia used to prepare and use IV drugs. Sharing these even once can cause transmission. Drug paraphernalia includes the cooker (bottle cap or spoon used to mix the drug), the cotton used in the cooker through which the drug is drawn up into the needle, the tourniquet used to tie up the arm, and the water used to mix with the drug. Transmission can occur by a needle stick in a health care setting to a health care worker. Although controversial, there may be a risk for transmission by sharing straws used to snort drugs such as cocaine.

The risk for sexual transmission is a controversial subject. There has been some research into this but not enough to well characterize the risk for sexual transmission. The risk of transmitting HCV from one person to another by sex is generally considered to be low, but it's important to bear in mind the potential exceptions. Among individuals in a monogamous relationship studies have shown there is a risk but it is very low. Among individuals who have been active sexually and have had multiple sex partners, the risk increases. It appears as though if an open sore from an STD such as herpes simplex is present this increases risk. If either sex partner has HIV the risk of HCV transmission increases. Anal sex may rupture membrane and may increase the risk for transmission. Sex during a woman's period may increase risk. Sex that may draw blood could increase risk. For a monogamous or married couple they should be informed that there is a potential risk but it is low. And they can discuss and decide upon the use of condoms. The CDC recommendations are that for such a couple a condom is not necessarily recommended. But for sexually active individuals condom use should be considered. Among men who have sex with men, several studies find an increased risk associated with risky sex behaviors such as rimming and fisting. Studies find HCV can be transmitted from a pregnant woman to the newborn. The risk of transmission of HCV was found to increase several times from 5% to about 18% when the woman has HIV. HCV has been found in semen and breastmilk but there is no evidence that it's transmissible in this way. I don't think there have been enough studies in regarding breastmilk to know for sure if it's transmissible that way, but caution may be advisable.

There are other potential routes of transmission that most experts feel have a low risk but they have not been well studied. These include tattooing, household transmissions (such as by sharing toothbrushes or razors where blood can be present), the razor in a barbershop, utensils in a nail salon. Of course, if proper sterilization is practiced and if clean utensiles are used risk can be eliminated, but proper sterilization is not used in certain of these circumstances. This discussion of potential routes of transmission is not exhaustive but I wanted to hit important points. As you can see there are many unanswered questions about how HCV is transmitted. It is hard to conduct the studies required to answer these questions for several reasons including because when the rates are relatively low and there are so many potential routes of transmission you would need large studies. In addition, some people are reluctant to be honest about or don't recall if they used an IVD one time.

Testing

Anti-HCV is detected by enzyme immunoassay (EIA). The third-generation test (EIA-3) used today is more sensitive and specific than previous ones. However, as with all enzyme immunoassays, false-positive results are occasionally a problem with the EIA-3. Additional or confirmatory testing is often helpful.

The best approach to confirm the diagnosis of hepatitis C is to test for HCV RNA (viral load) using a sensitive polymerase chain reaction (PCR) assay. The presence of HCV RNA in serum indicates an active infection. Testing for HCV RNA is also helpful in patients in whom EIA tests for anti-HCV are unreliable. For instance, immuno-compromised patients may test negative for anti-HCV despite having HCV infection because they may not produce enough antibodies for detection with EIA. Likewise, patients with acute hepatitis may test negative for anti-HCV when the physician first tests. Antibody is present in almost all patients by 1 month after onset of acute illness; thus, patients with acute hepatitis who initially test negative may need follow-up testing. In these situations, HCV RNA is usually present and confirms the diagnosis.

Recombinant Immunoblot Assay (RIA). Immunoblot assays are used to confirm anti-HCV reactivity, too. These tests are also called "Western blots". In some clinical situations, confirmatory testing by immunoblotting is helpful, such as for the person with anti-HCV detected by EIA who tests negative for HCV RNA. The EIA anti-HCV reactivity could represent a false-positive reaction, recovery from hepatitis C, or continued virus infection with levels of virus too low to be detected (the last occurs only rarely when sensitive PCR assays are used). If the immunoblot test for anti-HCV is positive, the patient has most likely recovered from hepatitis C and has persistent antibody virus. If the immunoblot test is negative, the EIA result was probably a false positive. Indeterminate RIA tests require further follow-up testing, including attempts to confirm the specificity by repeat testing for HCV RNA.

HCV RNA (PCR). Testing for HCV RNA is a reliable way of demonstrating that hepatitis C infection is present and is the most specific test for infection. Qualitative PCR amplification can detect low levels of HCV RNA in serum. Testing for HCV RNA is a reliable way of demonstrating that hepatitis C infection is present and is the most specific test for infection. Testing for HCV RNA by qualitative PCR is particularly useful when aminotransferases are normal or only slightly elevated, when anti-HCV is not present, or when several causes of liver disease are possible. This method also helps diagnose hepatitis C in people who are immunosuppressed, have recently had an organ transplant, or have chronic renal failure. A qualitative PCR assay made by Roche has now been approved by the Food and Drug Administration for general use. This assay will detect HCV RNA in serum down to a lower limit of 50 to 100 copies per milliliter which is equivalent to 25 to 50 international units. Almost all patients with chronic hepatitis C will test positive by this assay. The test result says a person is positive or negative, but does not tell the quantitative level of the viral load.

Several methods are available for measuring the titer or level of virus in serum (quantitative level), which is an indirect assessment of viral load. These methods include a quantitative PCR (Roche) and a branched DNA (bDNA) test (Chiron). The FDA approved a quantitative HCV viral load test from Bayer in April 2003. Unfortunately, these assays are not well standardized, and different methods from different laboratories can provide different results on the same specimen. In addition, serum levels of HCV RNA can vary spontaneously by 3- to 10-fold over time. Nevertheless, when performed carefully, quantitative assays provide important insights into the nature of hepatitis C. Most patients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per milliliter. Expressed as international units (IU), these averages are 50,000 to 5 million IU. National Genetics Institute (NGI) offers the HCV Superquant test. NGI/LabCorp offer a very sensitive quantitative test measuring as low as 2-10 IU/ml and up to as high as 100 million IU/ml.

Viral levels as measured by HCV RNA do not correlate with the severity of the hepatitis or with a poor prognosis (as in HIV infection); but viral load does correlate with the likelihood of a response to antiviral therapy. Rates of response to a course of alpha interferon and ribavirin are higher in patients with low levels of HCV RNA. There are several definitions of a "low level" of HCV RNA, but the usual definition is below 1 million international units (2 million copies) per milliliter (mL).

In addition, monitoring HCV RNA levels during the early phases of treatment may provide early information on the likelihood of a response. If viral load has not been reduced by 2 log or more at week 12, there is a low likelihood that a patient will achieve a sustained viral response. Discontinuation of therapy at week 12 or 24 can be considered if a 2 log reduction has not been achieved. Although recent studies suggest evaluation at week 12 is sufficient there is concern that this may be too soon and a 24 week evaluation may be more reliable. Some patients, particularly those with HIV, may take longer to achieve a 2 log response. Yet because of the shortcomings of the current assays for HCV RNA level, these tests are not always reliable guides to therapy. If a patient has advanced HCV, continuing therapy may be useful despite less than a 2 log reduction for the purpose of slowing HCV disease progression. Studies suggest that interferon has an anti-fibrotic effect that slows HCV disease progression for some patients.

Genotype. There are 6 known genotypes, 1-6. Knowing the genotype of a patient's HCV is important in making recommendations and counseling regarding therapy. Patients with genotype 2 or 3 are 2-3 times more likely to achieve a sustained viral response to interferon/ribavirin. The duration of combination therapy may be 24 weeks or 48 weeks and that decision may be based on whether a patient is genotype 1 or 2/3. There is no evidence yet that an HCV/HIV coinfected patient with genotype 2/3 should be treated for 6 months; it appears currently that 12 months treatment would be appropriate.

Diagnostic tests

All patients should be tested for their liver enzyme levels (ALT), HCV viral load, genotype, and a liver biopsy is recommended. The best way to evaluate a patient's disease is with a biopsy. Biopsy is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage in a patient. Radiologic testing such as with ultrasound cannot tell what disease stage a person has except for cirrhosis. Patients with HCV monoinfection who have normal ALT year after year usually have early HCV disease but 12% can have more advanced disease. In HIV-infected patients a higher percentage of patients can have normal ALT but have moderate or greater liver disease. So, ALT is not completely reliable in assessing the stage of liver disease, particularly in HIV-infected patients.

In HIV, the viral load predicts outcome. If a patient has a low viral load they should have a good outcome, if CD4s are adequate.

However in HCV, viral load does not predict outcome. A patient can have a low viral load and have cirrhosis. In HIV, a low viral load is 5,000 or 20,000 copies/ml. A high viral load is 100,000 copies/ml. In HCV, viral load below 2 million is considered low.

HCV causes the following changes in liver tissue and biopsy can help in seeing these changes:

--Necrosis (death or injury to cells) and inflammation around the portal areas (port of entry to liver), so-called "piecemeal necrosis" or "interface hepatitis."

--Necrosis of hepatocytes and focal inflammation in the liver parenchyma (connective tissue framework as opposed to tissues performing special functions of the liver).

--Inflammatory cells in the portal areas ("portal inflammation").

--Fibrosis, with early stages being confined to the portal tracts, intermediate stages being expansion of the portal tracts and bridging between portal areas or to the central area, and late stages being frank cirrhosis characterized by architectural disruption of the liver with fibrosis and regeneration.

The degree of inflammation and necrosis can be assessed as none, minimal, mild, moderate, or severe. The degree of fibrosis can be similarly assessed. Scoring systems are particularly helpful in clinical studies on chronic hepatitis.

Treatment for HCV mono-infection and co-infection

The therapy of chronic hepatitis C has evolved steadily since alpha interferon was first approved for use in this disease more than ten years ago. At the present time, the optimal regimen appears to be a 24- or 48-week course of the combination of pegylated alpha interferon and ribavirin.

Alpha interferon is a host protein that is made in response to viral infections and has natural antiviral activity. Recombinant (synthetically made in test tube) forms of alpha interferon have been produced, and several formulations (alfa-2a, alfa-2b, consensus interferon) are available as therapy of hepatitis C. These standard forms of interferon, however, are now being replaced by pegylated interferons (peginterferons). Peginterferon is alpha interferon that has been modified chemically by the addition of a large inert molecule of polyethylene glycol. Pegylation changes the uptake, distribution and excretion of interferon prolonging its half-life.

The development of pegylated interferon is an important advancement. Peginterferon can be given once weekly and provides a constant level of interferon in the blood, whereas standard interferon must be given several times weekly and provides intermittent and fluctuating levels. Interferon is administered by subcutaneous injection similar to how insulin is taken. More importantly, peginterferon is more active than standard interferon in inhibiting HCV and yields higher sustained response rates with similar side effects. Because of its ease of administration and better efficacy, peginterferon has been replacing standard interferon both as monotherapy as well as combination therapy for hepatitis C.

The accepted and preferred choice today for treatment is combination therapy with pegylated interferon plus ribavirin. Patients with HCV monoinfection and genotype non-1 can be treated for perhaps as little as 24 weeks. Patients with genotype 1 will need 48 weeks therapy. Although it has not yet been well researched, it is believed that patients co-infected with HIV will require 48 weeks therapy whether they have genotype 1 or 2. There is currently no evidence that co-infected patients should receive less than 48 weeks HCV therapy. Preliminary response rates from studies of HIV-infected patients show these patients don't respond quite as well to therapy as HCV monoinfected patients. It's been suggested that a longer duration of therapy may improve their response rates. An 18 month therapy study is ongoing.

Ribavirin is an oral antiviral agent that has activity against a broad range of viruses. By itself, ribavirin has little effect on HCV, but adding it to interferon increases the sustained response rate by two- to three-fold. For these reasons, combination therapy is now recommended for hepatitis C and interferon monotherapy is applied only when there are specific reasons not to use ribavirin. There are two FDA approved brands of ribavirin: Rebetol made by Schering-Plough and Copegus made by Roche. Current pricing for both ribavirins and for the two pegylated interferons are reviewed at the end of this paper.

Two forms of peginterferon have been developed and studied in large clinical trials:

Peginterferon alfa-2a (Pegasys: Hoffman La Roche: Nutley, NJ) and peginterferon alfa-2b (Pegintron: Schering-Plough Corporation, Kenilworth, NJ). Both are FDA approved. Peginterferon alfa-2a is given subcutaneously in a fixed dose of 180 mcg per week. Peginterferon alfa-2b is given subcutaneously weekly in doses of 1.5 mcg per kilogram per week (thus in the range of 75 to 150 mcg per week), so PegIntron is dosed by the patient weight. PegIntron is a powder and must be reconstituted by the patient by adding water. The water and powder come in 2 separate vials. Pegasys is provided in a liquid form in one vial. Pegasys

is stored in a refrigerator and PegIntron is stored at room temperature, as long as its not abnormally hot such as in Florida in the summer months.

Ribavirin is an oral medication, given twice a day in 200-mg capsules for a total daily dose of 800 to 1,200 mg based upon body weight and the form of peginterferon. In all situations, ribavirin is given in two divided doses daily.

Combination therapy leads to rapid improvements in serum ALT levels and disappearance of detectable HCV RNA in up to 80 percent of patients, depending on several factors including genotype, viral load, and stage of disease. Long-term improvement in hepatitis C disease occurs if HCV RNA disappears during therapy and stays undetectable once therapy is stopped (after 24 week follow-up period). Among patients who become HCV RNA negative during treatment, a proportion relapse when therapy is stopped. The relapse rate is lower in patients treated with combination therapy compared with monotherapy. Relapse rates appear higher when retreating prior combination nonresponders. Some studies have found that patients who are relapsers, nonresponders, and partial responders may achieve improvements in the condition of their liver, which in turn may slow disease progression. However, these findings have not been firmly established so ongoing studies are examining this further. It appears more likely that relapsers and partial responders will improve liver condition (inflammation, fibrosis). Nonresponders are patients who are unable to reduce viral load. Partial responders achieve a reduction in viral load while on therapy but viral load goes back up while still on therapy. The NIH HALT-C study is exploring this question but we may not have results for another 4 years. This study is giving Pegasys + ribavirin to patients who were previous nonresponders. If they do not achieve a response on Pegasys/RBV patients will be offered a half dose of Pegasys for ongoing maintenance therapy to see if disease progression is slowed.

Long-Term Viral Outcomes & Cure: For patients who maintain negative HCV RNA for 24 weeks after stopping HCV therapy, results from several studies show 98% remain HCV RNA negative. Several small studies following patients for up to 11 years show well over 90% remain HCV RNA negative. One or two small studies show that they could not find HCV in the liver cells of these patients who were negative in the blood. Based on information we so far have HCV is considered "curable". Longer-term clinical outcome studies can help to confirm this.

A 48-week course of combination therapy using peginterferon and ribavirin yields a sustained response rate of approximately 55 percent. A similar course of Pegasys monotherapy yielded in studies a sustained response rate as high as 35 percent. A response is considered "sustained" if HCV RNA remains undetectable for six months or more after stopping therapy.

The optimal duration of treatment varies depending on whether interferon monotherapy or combination therapy is used, as well as by HCV genotype. The patient's viral load before starting therapy also appears to be relevant to the response outcome. Patients with >2 million c/ml viral load have shown lower response rates than patients with <2 million c/ml viral load.

For patients treated with peginterferon monotherapy, a 48-week course is recommended, regardless of genotype. For patients treated with combination therapy, the optimal duration of treatment depends on viral genotype. Patients with genotypes 2 and 3 have a high rate of response to combination treatment (80 percent), and a study conducted with Pegasys and ribavirin found that a 24-week course of combination therapy yields results equivalent to those of a 48-week course regardless of HCV RNA. In contrast, patients with genotype 1 have a much lower rate of response to combination therapy, so a 48-week course yields a significantly better sustained response rate. Again, because of the variable responses to treatment, testing for HCV genotype is clinically useful when using combination therapy.

Three large studies have been conducted with pegylated interferon plus ribavirin in monoinfected patients. One study was conducted using PegIntron plus ribavirin. Two studies have been conducted using Pegasys plus ribavirin. These studies were used by the FDA for review of approval. In the PegIntron study (the Michael Manns led study) 29% of patients receiving PegIntron and ribavirin daily with genotype 1 and high viral load achieved a sustained viral response after 48 weeks treatment and a 24 week additional follow-up period. These patients received PegIntron 1.5 mcg/kg (weight-based dosed) once weekly by subcutaneous injection but only received 800 mg of ribavirin pills per day. Patients receiving interferon plus 1000/1200 mg ribavirin had a 28% sustained viral response. Patients receiving PegIntron plus ribavirin with genotype 1 and low viral load achieved a 72% sustained viral response rate, and these patients received PegIntron plus 800 mg daily of ribavirin. This reflects the effect of viral load on achieving a sustained viral response, when comparing the 72% to the 29% in genotype 1 with high viral load. Patients with genotype 2-6 receiving PegIntron plus 800 mg ribavirin had a 72% sustained viral response rate if they had high viral load and an 81% sustained viral response rate if they had a low viral load. Schering-Plough is currently conducting a prospective study exploring weight-based dosing of ribavirin as opposed to using just 800 mg per day.

There have been two large studies of Pegasys plus ribavirin in HCV monoinfected patients. In the study led by Michael Fried, patients received either Pegasys alone, standard interferon plus ribavirin, or Pegasys (180 mcg once weekly) plus ribavirin for 48 weeks with a 24 week follow-up period. Unlike the Manns study all patients received 1000 or 1200 mg of ribavirin. Among patients with high viral load and genotype 1, patients receiving Pegasys plus ribavirin achieved a better sustained viral response than patients receiving standard interferon plus ribavirin (41% vs 33%). Patients with low viral load and genotype 1 had a better sus-

tained viral response rate if they received Pegasys plus ribavirin (56% vs 44%). Patients with genotype 2/3 and high viral load had a 74% sustained viral response rate and patients with low viral load and genotype 2/3 had an 81% sustained viral response rate. This compared to a 59% sustained response rate in patients receiving interferon plus ribavirin with high viral load and genotype 2/3, and 65% for patients with low viral load and genotype 2/3. Some patients may not be able to tolerate ribavirin. In the Fried study, patients who received Pegasys alone achieved a 30% rate of sustained viral response.

In the second study patients received either 800 mg of ribavirin or 1000 or 1200 mg of ribavirin plus Pegasys. There was no comparison arm of interferon plus ribavirin in this study. This study found patients with genotype 2/3 had the same response rates regardless if they were treated for 24 or 48 weeks or if they received 800 or 1000/1200 mg ribavirin, and regardless of viral load. Patients with genotype 1 and high viral load and who received 800 mg ribavirin per day with Pegasys achieved a 35% sustained viral response rate. For genotype 1 patients receiving a higher dose of ribavirin (1000 or 1200 mg per day, based on patient weight), those with a high viral load (>2 million) were able to achieve a 46% sustained viral response rate with 48 weeks of therapy compared to patients with a low viral load (<2 million) who achieved a 61% sustained viral response rate. The sustained viral response rate for genotype 2/3 patients was 73-78% regardless of treatment duration (24 or 48 weeks), dose of ribavirin (800 vs 1000/1200 mg), and baseline viral load. In sum, this study found that these non-1 genotype patients could be treated for 24 weeks using 800 mg of ribavirin. This is important because 24 weeks of therapy is easier to tolerate than 48 weeks, and because 800 mg of ribavirin is easier to tolerate than 1000/1200 mg. Patients with compensated cirrhosis can respond well to therapy. Patients with compensated cirrhosis who received Pegasys plus 1000/1200 mg ribavirin for 48 weeks had 50% SVR vs 65% for non-cirrhotics.

It is generally accepted that you should not compare results of one study to the results of another study. Although the baseline characteristics of the patients in these 3 studies are similar, there can be differences between the patient groups in the studies. As well, the study designs, implementation, and interpretation of results can be different. So far, there have not been any head to head comparisons of the two pegylated interferons.

Early Viral Response Rule: stopping HCV therapy at week 12 or 24

Data has emerged from studies of peginterferon plus ribavirin supporting the idea of stopping therapy if an early response is not observed. The data is reported below and finds that if a patient does not achieve an early viral response it is unlikely they will achieve a sustained viral response. Therefore, HCV therapy could be discontinued. An exception might be in the case of maintenance therapy in patients with more advanced HCV disease in the hope that this may slow disease progression.

Michael Fried reported from his study of Pegasys on the predictive value of early virologic response (New England Journal of Medicine, 2002; 347:975-982). By week 12, 86% of patients (390 of 453) treated with peginterferon alfa-2a plus ribavirin had a virologic response, defined as a 2-log decrease from baseline HCV RNA levels (97 patients) or no detectable serum HCV RNA (293 patients). The absence of an early virologic response was not associated with early treatment discontinuation (before week 12) or dose modification. Of those with early virologic responses, 65 percent subsequently had a sustained virologic response. Those with no detectable HCV RNA by week 12 were more likely to have a sustained virologic response than those who had only a 2-log decrease in HCV RNA (221 of 293, 75% vs. 32 of 97, 32%). It appears as though patients with >80% adherence were more likely to achieve SVR compared to patients with <80% adherence. In contrast, among the 63 patients who did not have an early virologic response, 61 (97%) did not have a sustained virologic response.

Gary Davis reported similar findings from the Michael Manns study of pegylated interferon alfa-2b plus ribavirin (Hepatology, November 2002; part 2, volume 36, number 5). Davis reported that data from 2 large clinical trials of peginterferon and ribavirin were combined and analyzed to determine the optimal definition of an EVR which, if not achieved, was associated with a low likelihood of a sustained virological response (SVR). A fall in HCV RNA level to undetectable or by at least 2 log10 units after 12 weeks was found to be the optimal definition of an EVR. Among 965 patients, 778 (80%) achieved an EVR by week 12, including all except 1 patient with genotypes 2 or 3. 68% of patients who achieved an optimally defined EVR had an SVR. Among 187 patients without an EVR, only 3 (1.6%) had an SVR. These findings "suggest that patients with genotype 1 who do not achieve an EVR should stop treatment after 12 weeks. Use of an early stopping rule reduces treatment costs by at least 16% and avoids the inconvenience and side effects of treatment in the 19% of patients without an EVR who have little chance of a lasting virological response".

SVRs were achieved in 80% of patients who were HCV RNA negative at week 12 of treatment, but in only 40% in those who had a 2 log10 unit decline in HCV RNA level while remaining HCV RNA positive. The majority of subjects with an EVR (greater than a 2 log10 unit decrease) at 12 weeks were HCV RNA negative (89%). At issue is whether the 11% of patients who achieve an EVR by 12 weeks but are still HCV RNA positive should be retested at 24 weeks to assess continued positivity and whether this reliably predicts nonresponse. Further analysis was available from the peginterferon alfa-2b trial on patients who had a 2 log10 unit decline in viral levels but were still HCV RNA positive at 12 weeks. Among 23 such patients, 13 were HCV RNA negative at week 24, and 6 of these patients subsequently had an SVR; in contrast, 10 patients were still HCV RNA positive at 24 weeks, and none had an SVR.

Although the number of subjects in these subgroups was small, "these observations suggest that patients with a 12-week EVR who are still HCV RNA positive should be retested for HCV RNA by a sensitive qualitative PCR at week 24 of treatment and stop treatment if they remain HCV RNA positive". This secondary decision point would allow for early discontinuation of therapy in a further proportion of patients.

Therapy in HIV co-infection

Several studies were conducted a number of years ago finding co-infected patients responded as well to therapy as mono-infected patients. These studies were not well conducted and were small. More recently conducted studies, which are better designed, are showing preliminary data suggesting that co-infected patients may experience reduced rates of sustained viral response to HCV therapy compared to monoinfected patients. Co-infected patients may not respond as well to therapy as mono-infected patients, but co-infected patients can clearly respond well to therapy. This reduced response may be due to the impaired immune system caused by HIV. An additional concern is the ability of co-infected patients to maintain adherence to HCV therapy. Co-infected patients may experience more side effects and adverse events, and may have more difficulty tolerating therapy. These patients may be more likely to experience anemia and reduced white or red blood cells. Studies show the use of Procrit can increase hemoglobin, reduce fatigue, and maintain higher dosing of ribavirin. This may be crucial in providing an optimal opportunity to patients to achieve a sustained viral response rate. As well, a disproportionate percentage of co-infected patients are African-Americans and studies find that greater than 90% have genotype 1. Patients with genotype 1 have a lower rate of response to therapy. One study showed that African-Americans with genotype 1 experienced lower response rates than Caucasians with genotype 1, so reduced response may not be due just to genotype. Co-infected patients with a history of drug use may have issues with depression or psychiatric conditions. A psychiatric evaluation before starting therapy is important, and the use of anti-depressants can greatly help in addressing the development of depression on therapy and in improving adherence and viral response rates.

Several large studies in co-infected patients are ongoing. ACTG 5071 is a moderately sized study in which patients are receiving either Pegasys plus ribavirin or standard interferon plus ribavirin. After 24 weeks of therapy, patients receiving Pegasys plus ribavirin had a much better response (44% undetectable viral load vs 15%). The 44% response rate was less than would be expected to be seen in HCV monoinfected patients. However, ribavirin was dose escalated starting with 600 mg per day. This was done to make therapy more tolerable and prevent study discontinuation of patients. This may have affected the response rates. We await final study results. Roche is conducting 2 large co-infection studies using Pegasys + ribavirin in the US and internationally, but we don't have results yet. There are additional moderately sized ongoing studies in co-infected patients including the examination of PegIntron and ribavirin.

A French study of 400 co-infected individuals reported preliminary results in 2003. At the end of 48 weeks of therapy with PegIntron plus 800 mg of ribavirin/day 44% of patients had undetectable viral load (<100 copies/ml) compared to 27% of patients receiving interferon (standard dosing) plus 800 mg ribavirin/day. These rates are lower than observed in studies in monoinfected patients. Treatment was discontinued in 30% of patients and severe adverse events occurred in 24% of patients. A significant decrease was observed at the early stage of treatment (week 12) in hemoglobin, lymphocytes and more marked with PEG-IFN for neutrophils and platelets. In a small Spanish study of 68 co-infected patients, who received PegIntron plus 800 mg/ribavirin/day or standard interferon plus 800 mg/ribavirin/day, the sustained response rate was 42% for patients receiving PegIntron regimen and 33% for the patients receiving standard interferon regimen. These rates of response are lower than that seen in studies of monoinfected patients.

Bear in mind that adherence to taking therapy is important in HCV just as it is in HIV therapy. The more adherent a patient is to taking the medications the better the response rates. Studies show that adherence of greater than 80% shows a better response rate than for patients with <80% adherence. 80% adherence means taking > 80% of the weekly interferon injections and ribavirin pills. Studies also show that patients taking >90% of the medications had a better response rate than patients taking 80% of the medications.

Side effects, adverse events and tolerability of HCV therapy

Another important point for consideration is the tolerability of the drugs. These therapies for HCV can be difficult to tolerate. Patients may be discouraged from staying on therapy if they cannot tolerate the drugs. Obviously, if they don't stay on therapy they cannot achieve a positive outcome. Side effects and adverse events can be significant. Side effects can include fatigue, irritability, emotional distress, weight loss, and depression. Adverse events can include anemia, reduced red and white blood cell counts, and reduced platelet counts.

Most patients experience some of these side effects and have a varying degree of difficulty with tolerating the therapy. Most patients fall in the middle in terms of how much difficulty they have in tolerability of therapy. A small percentage do not have a problem with the side effects and a small percentage of patients will have extreme difficulty with them. The degree of difficulty in expe-

riencing the side effects varies by individual. Many of these side effects are mild to moderate in severity and can be managed and tolerated. Side effects may diminish after the first few weeks of therapy. Non steriodal anti-inflammatory drugs (NSAIDs) such as Advil can be helpful for the muscle aches and low-grade fever. Vioxx, an arthritis drug, can be helpful. Clinically depressed patients may not be candidates for HCV therapy. This is an evaluation to be conducted by the doctor. However, less serious depression can be managed. Fatigue and depression are occasionally so troublesome that the dose of interferon may have to be decreased or therapy stopped early. But recently conducted preliminary research of drug therapy for this problem has found that EPO (Procrit) for anemia may avoid dose reduction or stopping therapy by improving hemoglobin. GCSF may be used to treat neuropenia. Depression often can be managed by use of anti-depressants. Depression and personality changes can occur on interferon therapy and be quite subtle and not readily admitted by the patient. These side effects need careful monitoring. It is helpful for the patient's family or spouse to be called into a meeting with the doctor to apprise them of what side effects the patient may exhibit, particularly the irritability, emotional distress, fatigue, and depression. Support groups can be helpful in helping patients in their decision to accept therapy and during therapy.

Ribavirin causes a dose-related hemolysis of red cells; with combination therapy, hemoglobin usually decreases by 2 to 3 g/dL and the hematocrit by 5 to 10 percent. The amount of decrease in hemoglobin is highly variable. The decrease starts between weeks 1 and 4 of therapy and can be precipitous. Some patients develop symptoms of anemia, including fatigue, shortness of breath, palpitations, and headache.

The sudden drop in hemoglobin can precipitate angina pectoris in susceptible people, and fatalities from acute myocardial infarction and stroke have been reported in patients receiving combination therapy for hepatitis C. For these important reasons, ribavirin should not be used in patients with preexisting anemia or with significant coronary or cerebral vascular disease. If such patients require therapy for hepatitis C, they should receive interferon monotherapy.

Combination therapy with pegylated interferon plus ribavirin can uncommonly cause marked reduction in platelets (thrombocytopenia), and neutropenia (neurtophils, a type of white blood cell). These adverse events including anemia may be slightly more common in HIV-infected patients. More uncommonly, therapy can cause autoimmune disease (particularly thyroid disease), and suicidal ideation or attempts. For these reasons patients are instructed to make weekly visits to their doctor upon initiation of therapy for 4 weeks. After the first month visits can lessen to every 2 and then every 4 weeks. It's important for the patient to inform the doctor of all experiences they are having.

A unique but rare side effect is paradoxical worsening of the disease. Because of this possibility, aminotransferases (liver enzymes) should be monitored. If ALT levels rise to greater than twice the baseline values, therapy should be stopped and the patient monitored. Some patients with this complication have required corticosteroid therapy to control the hepatitis.

Retreatment and maintenance therapy

What is the response to pegylated interferon for patients who were previously treated with interferon plus ribavirin but were not able to achieve a sustained response? Studies show that combination interferon/ribavirin nonresponders can be successfully retreated with peginterferon/ribavirin. Ongoing research studies find response rates of 11-15% for previous non-responders. Response to retreatment will be better for relapsers and partial responders than for non-responders. Non-responders to interferon monotherapy will respond better to retreatment with pegylated interferon plus ribavirin than nonresponders who received interferon plus ribavirin.

What is maintenance therapy? For patients who are unable to achieve a sustained viral response but have advanced disease "maintenance therapy" is a serious consideration. Patients can continue on a half dose of pegylated interferon in the hopes that interferon will slow disease progression until new drugs are developed. The results of a number of studies show that interferon slows disease progression in some patients, but these studies are not conclusive and doubts (particularly in nonresponders) about the ability of interferon to do this linger. So it's expected that the ongoing HALT-C study, mentioned above, will answer the question. In the meantime results from this study are not expected for 4 years and doctors are using maintenance therapy for patients with no other options. The ability of the patient to tolerate interferon should be considered.

Outcomes of therapy

Achieving a sustained response for the person without cirrhosis should prevent progression of the disease. If a person has cirrhosis will achieving a sustained viral response prevent progression to cancer and decompensated liver disease? It should but we don't know for sure, so monitoring is appropriate. Several studies already conducted provide evidence that interferon use in patients with cirrhosis and nonresponders can slow or reverse disease progression. A French study reported this finding at the AASLD liver conference in the Fall of 2002, and study results can be read on the NATAP website in the Conference Reports section. These results certainly support the notion that patients with cirrhosis who achieve a sustained viral response have a good chance of stopping and perhaps reversing disease progression. But some scientists are not convinced yet, so we need more studies to look at

this question. The HALT-C study may provide information on this question.

Who should be treated?

The recent NIH HCV Consensus conference panel of experts recommended that patients at risk for disease progression should be offered treatment. This 2002 conference however expanded their definitions of who should be recommended for treatment. The old 1997 conference panel recommended that all patients with fibrosis or moderate to severe degrees of inflammation and necrosis on liver biopsy should be treated and that patients with less severe histological disease be managed on an individual basis. Patient selection should not be based on the presence or absence of symptoms, the mode of acquisition, the genotype of HCV RNA, or serum HCV RNA levels. In the 1997 recommendations the panel were somewhat restrained or lukewarm in the strength of recommendations to treat patients with HIV. Regarding HIV, although they did not discourage treatment they said "the efficacy of combination therapy in HIV-infected people has been tested in only a small number of patients". The 1997 panel said therapy was contraindicated for active substance abuse, but the 2002 draft recommendations are clearly more supportive for treating these patient groups.

The 2002 draft recommendations said (they are available for reading on the NATAP website):

Injection drug users(Intravenous drug users-IVDU's)

Recent experience has demonstrated the feasibility and effectiveness of treating HCV in people who use illicit injection drugs (known as injection drug users or IDUs). This is important because IDUs comprise the largest group of hepatitis C patients in the United States, and successful treatment may reduce transmission. Management of HCV-infected IDUs is enhanced by linking IDUs to drug-treatment programs. Efforts should be made to promote collaboration between experts in HCV and substance-abuse providers. HCV therapy has been successful even when the patients have not been abstinent from continued drug use or are on daily methadone. Few data are available on HCV treatment in active IDUs who are not in drug treatment programs. We need support systems for these patients, and we need studies to explore the types of systems that may be more successful and to establish that they can work. A recent study from Diana Sylvestri, MD (OASIS Clinic, Oakland, CA) reported at the 2002 DDW conference found patients on methadone maintenance who received group support could respond well to HCV therapy even if they experienced a brief relapse to IVDU. Timely intervention due to close monitoring through group support can stem the relapse and these patients could achieve a sustained viral response.

HIV co-infection

All HIV infected persons should be screened for HCV. Patients with chronic hepatitis C and concurrent HIV infection may have an accelerated course of HCV disease. Therefore, although there are no HCV therapies specifically approved for patients co-infected with HIV yet, these patients should be considered for treatment. Thus far, studies have enrolled only patients with stable HIV infection and well-compensated liver disease. In co-infected persons, an SVR can be achieved with HCV treatment. Although treatment of HCV has not jeopardized control of the HIV infection, additional data are needed. In his report to the panel, David Thomas, MD, (Johns Hopkins University Medical School) strongly recommended that patients with HIV receive equal and adequate access to care and treatment for HCV. He made reference to that there are pockets of areas in the US where HIV-infected patients are not being tested for HCV.

New treatments

Information from an early phase I study was reported at the AASLD liver conference in November 2002 on the first HCV protease inhibitor. The study was conducted in HCV+ patients. This study was preliminary and patients received the drug (BILN 2061) for 48 hours. The drug exhibited potency as HCV viral load decreased 2-3 logs by 48 hours and there did not appear to be safety concerns. This study provided proof of concept that HCV protease inhibitors can be effective. Additional HCV protease inhibitors are in early stages of development. Polymerase inhibitors for HCV are in early stages of development. Helicase inhibitors are receiving research attention. Also, anti-fibrotic agents which may not have antiviral effect are in early stages of development.

HCV/HIV Co-infection Policy and Research Direction
By Jules Levin

I've been following this field closely for several years, recognizing co-infection with HCV was emerging as a major concern. Many in the medical, patient, government and service provider community still haven't fully realized the impact and potential impact HCV will or may have on HIV-infected patients. Several small and large studies suggest HCV may be the leading cause of death in HIV. A number of studies show HIV accelerates HCV progression but we don't have clear characterization of this nor do we understand well the natural history or course of progression of HCV in co-infected patients. In addition, there is little prevalence data on how many people have HCV and co-infection.

I have been advocating and speaking out for several years on the key issues our affected communities need to focus on improving, and these areas have not changed nor has adequate attention been paid. Areas of research and policy in co-infection where we need to step up attention include:

--HCV and lipodystrophy, metabolics, bone loss, and diabetes. A few small studies show coinfected patients have higher risk compared to HIV-infected individuals for metabolic abnormalities, diabetes/insulin resistance, and lipodystrophy. HIV-infected patients are experiencing higher rates of bone loss and diabetes than HIV-negative individuals. As well, HCV is associated with bone loss and fatty liver and diabetes. This needs additional research attention. As David Thomas, MD, from Johns Hopkins Medical School, said in his talk on co-infection at the NIH HCV Consensus Conference, all areas of co-infection receive too little research attention.

--Should HCV or HIV therapy be started first? When should HIV-infected patient begin HCV therapy? It has been clear to me and others for 2 years that it may be appropriate to consider HCV therapy first in the right circumstances. But this needs research attention.

--What is affect of HIV HAART medications and hepatotoxicity on liver disease progression? We don't have adequate answers to this question and this is an important area of research needing attention. There is an ongoing initial study trying to examine this question. The best way to try to answer this question is pre- and post biopsy with HAART. Perform a biopsy before starting HAART and after being on HAART for a period of time.

--What do we do with special populations? A number of co-infected patients will be therapy nonresponders. African Americans respond less well to HCV therapy; but we don't understand why. An NIH study is examining this question. We have little data on response to therapy by Hispanics. What is the role of maintenance therapy in co-infection? We need research on these questions.

--How does HIV impair the immune response to HCV and what is the affect of HIV on response to HCV therapy? Some research into these areas have started. But we need to bolster and expand this research.

--How can we provide better access and care to former and current injection drug users, considering injection drug use is now the leading cause for transmission of new HCV infections.

--There are potentially tremendous gaps in access to care & therapy for coinfected patients. Right now only 7 ADAPs (AIDS Drug Assistance Programs) are covering HCV therapy. Increased ADAP funding is important. Studies show co-infected patients are not readily accessing the Hep A vaccine or perhaps the Hep B vaccine. There are gaps in access to proper diagnostic testing: HCV viral load, genotype testing, and liver biopsy are not readily available and reimbursable to all.

--Who will provide care to co-infected patients? The education level of HIV treating physicians in general about treating HCV is severely lacking right now. HCV treaters are not prepared to treat the HIV-infected communities. The shear numbers of co-infected patients and the patient populations are not easily absorbed by HCV treaters or the healthcare system. The HIV community of patients, educators, advocates, and service providers do not in general fully understand or recognize the problems related to co-infection, so education is required. We have not begun to discuss a model for treating coinfected patients. A few hospital and clinic sites have implemented useful models, but on the whole few are discussing this.

--Most co-infected patients are African-Americans, IVDUs and Hispanics. This has tremendous implications for care, treatment, education, and reimbursement.

--Management & tolerability of side effects and toxicities may be more difficult for some coinfected patients. We need to research better understanding of this for the goal of improving adherence and response to therapy.

--Co-infection is a different and more difficult disease in a number of important ways from HCV. Support services needed for co-infected patients will be different but there has been little discussion and commitment about what the needs are & how to fund these programs. Special support groups, adherence programs, and services regarding self-injection for interferon are needed.

--A high proportion of IVDUs have HCV. It's estimated that 70% of patients on Methadone Maintenance have HCV, and 60-90% of those HIV-infected through IVDU have HCV. And we need programs to address these needs. Programs are needed for testing and counseling, prevention, and specialized care. As well, education for doctors, patients, and service providers are needed. HCV was recognized at the recent NIH Consensus Conference as an epidemic.

--There are not enough doctors to care for HCV monoinfected patients and certainly for HIV/HCV co-infected patients.

In the end, we need new drugs to manage & treat HCV. We need to encourage and reinforce drug research.

This list on policy & care issues is not meant to be exhaustive but highlights key concerns.

The recent NIH HCV Consensus Development Conference supported several important positions but as the Conference organizers said themselves their recommendations are not mandates but merely recommendations. Here are some key recommendations by the panel:

1. HIV positive patients should have access to care and receive treatment for HCV

2. IVDUs can respond well to HCV therapy in the right circumstances. The support this notion the panel recommended collaborations between the medical community and the community of service providers working with IVDUs would help promote creating & developing these circumstances.

3. Prisoners with HCV ought to receive attention in terms of receiving testing, care & treatment.

4. The panel recommended the establishment of an HCV Clinical Trials Group similar to the ACTG for HIV.

Thanks to the National Institute of Diabetes & Digestive & Kidney Diseases of the NIH (NIDDK). Prepared by Jules Levin, NATAP

Costs and Access to Treatment and Diagnostic Testing for Hepatitis C

Without access to care and treatment the best treatments in the world are not helpful. Many HCV/HIV co-infected patients have difficulty in accessing pegylated interferon and ribavirin. The HIV care system is burdened with providing expensive treatments and care to a large number of HIV-infected individuals. State ADAPs are currently under funded. As a result, in addition to restrictions in access to pegylated interferon, many patients face restrictions to access diagnostic testing for hepatitis C (HCV genotype, viral load). Currently, some state AIDS Drug Assistance Programs (ADAP) programs are not covering or reimbursing for pegylated interferon plus ribavirin therapy HCV-RNA viral load. As well, properly conducted biopsies are not always covered. This places a significant burden on patients, clinics, and hospitals. Often clinics and hospitals are unable to get reimbursement for diagnostic tests and are forced to pay for them out of their own budget, or may even be unable to provide the tests for patients. In the tables at the bottom of this page are comparative prices for the drugs used to treat hepatitis C virus, showing a significant price difference between the two pegylated interferons and the two FDA approved ribavirins.

There are also gaps in access to treatment and care for HCV monoinfected individuals. Private insurers do not always reimburse for optimal treatment and patient care. HCV-infected individuals with low or limited incomes are at times unable to pay for treatment and care. Patients who are prior non-responders to interferon and ribavirin are sometimes denied coverage for pegylated interferon plus ribavirin.

The standard of care today for hepatitis C is pegylated interferon plus ribavirin. For patients infected with the hepatitis C virus, pegylated interferon and ribavirin combination therapy has improved response rates and is more convenient to administer compared to the old version of interferon plus ribavirin.

Here is a listing of the disparity in pricing between both pegylated interferons and ribavirins. The average wholesale price (AWP) is the amount the wholesaler charges retail pharmacies for a drug. The first table below is the AWP for a one month supply of drug. Table 2 provides costs for 4, 24, and 48 weeks of combination therapy using ribavirin dose of 800 or 1200mg per day. Some patients, however, may be prescribed 1000 mg per day of ribavirin. Rebetol is the brand name for Schering Plough's ribavirin, and Copegus is the brand name for Roche's ribavirin.

You will see in the Tables below pricing for PegIntron by the amount of drug in the vial,150 mcg and PegIntron 120 mcg. PegIntron is sold in 4 different vial sizes: 150 mcg, 120 mcg, 80 mcg, and 50 mcg. PegIntron is dosed by the weight of the patient, so the more the weight of a patient the higher the dose that is needed of PegIntron. The most commonly prescribed vials are the 150 mcg and 120 mcg dose vials. For example, since PegIntron is recommended to be dosed at 1.5 mcg per kilogram (1 kg =2.2 lbs) of a person's total weight, a 180 pound (81.8 kg) patient will be prescribed 122.7 mcg for their weekly injection (81.8 kg x 1.5 mcg).

Table 1. COST FOR ONE MONTH SUPPLY

RIBAVIRIN

	800 mg	Difference	1200 mg	Difference
Copegus	$708	-$527	$1063	
Rebetol	$1235		$1854	+$791/month

PEGYLATED INTERFERON

	Weekly Dose	Price	Difference
PegIntron	150 mcg	$1628*	+$173
PegIntron	120 mcg	$1550*	+$95
Pegasys	180 mcg	$1455	

* This price reflects a 7% AWP increase since March 2003.

Table 2. COST OF PEGYLATED INTERFERON + RIBAVIRIN

	1 month	24 weeks	48 weeks	Difference
Pegasys + Copegus 800mg	$2163	$12,978	$25,956	
PegIntron (150 mcg) + Rebetol 800 mg	$2863	$17,178	$34,356	+$8,400
PegIntron (120 mcg) + Rebetol 800mg	$2785	$16,710	$33,420	+$7,464
Pegasys + Copegus 1200 mg	$2518	$15,108	$30,216	
PegIntron (150 mcg) + Rebetol 1200 mg	$3482	$20,892	$41,784	+$11,568
PegIntron (120 mcg) + Rebetol 1200 mg	$3404	$20,424	$40,848	+$10,636

Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease

Liver Transplantation March 2003, Volume 9, Number 3. Guy Neff et al, including Eugene Schiff, John Fung, Margaret Ragni, Dushyantha Jayaweera. Departments of Medicine and Surgery, Division of GI Transplant, University of Miami, Miami, FL; and the Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA.

The authors say: "OLT is effective in selected HIV-positive patients..., more liberal application of OLT in selected HIV candidates be considered..most centers continue to exclude the HIV population from OLT as a possible life-saving measure without sufficient objective information to support these practices. Without an OLT, patients with HIV and significant liver disease will not survive... we should consider HIV-positive patients who have extenuating circumstances, with detectable HIV viral loads before OLT when they may not be able to tolerate potent antiretroviral medications in the presence of significant liver dysfunction." This article is posted on the NATAP website http://www.natap.org.

Summary: Patients with human immunodeficiency virus (HIV) most often have hepatitis C virus (HCV) or hepatitis B (HBV) virus - co-infection, or both, as a cause of their liver disease. Recent survival statistics show that patients infected with HIV treated with highly active antiretroviral therapy (HAART) can expect a significant prolongation of life by interfering with the natural progression of HIV to aquired immune deficiency syndrome (AIDS). Therefore, HIV-positive patients experiencing complications of liver failure are at greater immediate risk of dying from their end-stage liver disease (ESLD) rather than their HIV.

Many transplant centers still consider HIV infection as a contraindication for orthotopic liver transplantation (OLT). At our two institutions, we believe that patients with HIV suffering from ESLD should be considered for OLT. This study evaluates the survival of patients undergoing OLT with HIV under HAART therapy. OLT was performed in 16 patients with HIV suffering from ESLD as a result of chronic HCV, chronic HBV, or fulminant hepatic failure (FHF). Collected data include patient demographics, patient and graft survival, pre-OLT assessments, and postoperative complications (including opportunistic infections). Ten patients at Pittsburgh and 6 patients at Miami received OLT. Of the 16 patients who received OLT, 14 remain alive to date. Thirteen of 16 patients are more than 12 months post-OLT, whereas the last patient is currently 6 months post-OLT. Five patients at Miami and 9 of 10 patients at Pittsburgh received HAART therapy before OLT, although 2 of the Pittsburgh patients had their HAART therapy discontinued before OLT because of significant liver dysfunction.

The pre-OLT viral loads were undetectable in 13 of 16 patients. The cluster determinant (CD)4 count was less than 200 in 6 patients and greater than 100 in 2 patients before OLT. In all patients, CD4 counts increased above 200 in the post-OLT period. Tacrolimus toxicity associated with the pharmacologic inhibition of cytochrome p450 metabolism caused by protease inhibitors occurred in 6 patients after OLT. Six patients (38%) experienced acute cellular rejection immediately after OLT. Our experience suggests that OLT is effective in selected HIV-positive patients suffering from ESLD. Patient and graft survival was similar to non-HIV-positive patients suffering from the same indications for OLT. Acute cellular rejection was no less frequent that seen in non-HIV-positive patients. Given the complex pharmacologic interactions between the protease inhibitors and tacrolimus, careful monitoring, and attention is required to prevent toxicity or underdosing.

Background: Orthotopic liver transplantation (OLT) has advanced markedly since its introduction in 1964. One-year survival rates, 30% in the 1970s under azathioprine immunosuppression, are now well above 80%. The improved survival rates are the result of advances in patient selection, posttransplant management, immunosuppression, and antiviral prophylaxis. This has led to reevaluation of the original contraindications to surgery and broadening the spectrum of patients who should be considered for OLT.

Until recently, one concurrent illness considered by many to be an absolute contraindication for OLT is the presence of human immunodeficiency virus (HIV). However, the introduction of highly active antiretroviral therapy (HAART) has resulted in a dramatic improvement in the survival of patients infected with HIV. Thus, the prevalence of HIV patients co-infected with hepatitis C virus (HCV), hepatitis B virus (HBV), or both, who present with end-stage liver disease (ESLD) is increasing. HIV co-infected patients tend to suffer from an aggressive HCV course, thus resulting in liver failure at a faster rate when compared with individuals without co-infection. In addition, almost all of the antiretroviral agents used for the treatment of HIV are metabolized in the liver. Patients with hepatic metabolic impairment cannot use these agents, resulting in increased mortality associated with aquired immune deficiency syndrome (AIDS).

The success with HAART regimens has uncovered a dilemma, namely patients with HIV dying secondary to ESLD. In fact, associated liver failure in co-infected HIV positive patients is one of the leading causes of death in men between the ages of 25 and 44 years. Whereas OLT is considered a standard therapeutic modality for the treatment of nearly all ESLD, patients with HIV generally have been excluded despite the improvement in survival since the implementation of the HAART regimen. This exclusion is a result of the pre-HAART fears of disease progression and the scarcity of organs. It is possible that death in many of these patients may be prevented if OLT could be shown to have a similar utility to non-HIV OLT recipients.

We retrospectively analyzed a group of patients infected with HIV from the University of Miami (UM) and the University of Pittsburgh (UPMC) transplant centers with ESLD that received OLT in the HAART era. The purpose of this analysis is to describe the management strategies, survival, and drug interactions when HIV infected patients with liver failure undergo OLT.

All patients with HIV and ESLD who underwent OLT at UM and UPMC liver transplant centers between September, 1997, and December, 2001, were reviewed. The information was obtained in a standardized manner with an extraction form. The standard treatment post-OLT for non-HIV patients included tacrolimus, administered to maintain a 12-hour trough level of 8 to 12 ng/mL, corticosteroids tapered to discontinuation by week 12, a proton pump inhibitor for acid suppression, and sulfamethoxazole/trimethoprim prophylaxis against Pneumocystis carinii. The HIV OLT population received the same treatment except for adjusted serum levels of tacrolimus when protease inhibitors (PIs) were initiated; target levels for 24 hours was 5 to 7 ng/mL. Prophylaxis for cytomegalovirus (CMV) and herpes simplex virus (HSV) was performed in standard fashion with gancyclovir, acyclovir, or both.

HAART therapy was individualized based on known response and resistance patterns. In all OLT patients in this series, HAART consisted of a Pis with one or two nucleoside reverse transcriptase inhibitors. These were started when liver functions returned close to normal and when oral intake was satisfactorily resumed, usually by the second post-transplant week.

A total of 16 patients with ESLD received OLT, 6 at UM (cases 1 through 6) and 10 at UPMC (cases 7 through 16). Two were African-American and 3 were female. Age ranged from 40-67.

Eleven patients had ESLD secondary to HCV infection (1 with concomitant HCC), 3 with ESLD secondary to chronic HBV infection, and 2 patients with fulminant hepatic failure (FHF); 2 patients had HCV & HBV. The two deceased patients had HCv & hemophilia dying at 12 days and 570 post-transplant, respectively. The etiology of FHF in 1 patient was presumably because of toxicity of nucleoside analogs used for HIV therapy and the other with acute HBV. All patients were listed for OLT as outlined by United Network of Organ Sharing (UNOS). All patients were listed and transplanted using the status designation that existed before implementation of model for end-stage liver disease (MELD) in March, 2002: status 1, acute liver failure; status 2A, chronic liver disease with expected survival of less than 7 days; status 2B, chronic liver disease with expected survival of more than 7 days.

Patient summaries: University of Miami (UM)

The first HIV-positive OLT recipient at UM suffering from cirrhosis secondary to chronic HBV occurred in March of 1999. The HAART regimen consisted of nevirapine, lamivudine, and abacavir sulfate and was continued postoperatively. His post-transplant course was complicated by HSV-zoster at month 4, treated with acyclovir. The infection was believed the result of overimmunosuppression and his tacrolimus was lowered. He subsequently experienced an episode of acute cellular rejection (ACR) that responded to steroid pulses. His HIV status has remained stable, HIV viral load undetectable, and the CD4 count returned to greater than 1,000. The HBV has remained DNA-negative since OLT while treated with lamivudine.

The second HIV-positive OLT recipient also had chronic HBV and underwent transplantation in February, 2000. He was maintained on the following HBV therapy and HAART regimen: lamivudine, zidovudine, and nevirapine. He developed a biopsy-proven ACR 4 days after OLT that required muromonab-CD3 therapy. The HIV viral load has remained undetectable, and the CD4 count has returned to more than 400. Approximately 20 months after transplant, he developed an HBV lamivudine mutant that was treated with tenofovir and is currently HBV DNA-negative.

The third OLT HIV-positive recipient was a Haitian man who presented to the emergency room with fulminant HBV requiring OLT in August, 2000. This patient was naive to antiretroviral medications at the time of presentation. He was started on lamivudine for the treatment of HBV and after OLT on zidovudine and nelfinavir mesylate for HIV. His post-OLT course has been complicated by an unexpected drug interaction with ritonivir that resulted in toxic levels of tacrolimus. The patient was given a standard post-transplant dose of 3 mg of tacrolimus that resulted in a level of 50 ng/mL. At 12 weeks, he developed biopsy-proven ACR, managed with steroid therapy. He has remained HBV DNA-negative since transplantation. The HIV status required HAART management adjustment from lamivudine, zidovudine, and nelfinavir mesylate to lamivudine, zidovudine, and efavirenz at week 48, because his HIV viral load reached 6,000 copies/mL particles. The viral load has since become undetectable with the HAART regimen adjustments.

The fourth HIV-positive OLT candidate underwent transplantation in September, 2000, secondary to HCV-related cirrhosis. Her HAART regimen included zidovudine, lamivudine, and nevirapine. The post-operative medical course was complicated by a ritonavir interaction and subsequent tacrolimus toxicity. The tacrolimus was decreased to 0.25 mg every fourth day. Lopinavir was used to replace ritonivir as a result of clinical hepatitis with abnormal transaminases two times greater than normal. Two months later, a liver biopsy specimen showed marked steatosis, and lopinavir was replaced with amprenavir. Her HAART regimen required several adjustments and is currently zidovudine, lamivudine, abacavir, and tenofovir. The HCV recurrence was seen at week 8 with positive RNA PCR test results of 15 million copies/mL and an elevation of her liver chemistries 1.5 times normal. Liver histology revealed moderate inflammation, and the patient was placed on pegylated interferon alfa 2b with ribavirin therapy. Histology at after 12 months of interferon and ribavirin therapy revealed a slight reduction in inflammation but stage 2 fibrosis (stage 1, portal fibro-

sis; stage 2, few bridges; stage 3, many bridges; stage 4, cirrhosis).

The fifth HIV-positive patient received his OLT in October, 2000 for cirrhosis related to chronic HCV. The HAART regimen has been maintained with efavirenz, lamivudine, and zidovudine. The HCV after OLT recurred based on histology and PCR detection at week 12. He was started on pegylated interferon alfa 2b and ribavirin with resultant marked decrease in the HCV PCR to 300,000 IU/mL from 2 million IU/mL and improved inflammation score. His HIV status, including viral load, has been undetectable, and his CD4 count has reached 350. Liver biopsy at 24 months showed mild inflammation and stage 2 fibrosis.

The sixth HIV-positive case at UM was a woman requiring repeat OLT because of chronic rejection. The first transplant was performed for HCV cirrhosis. Her HAART regimen is maintained with efavirenz, lamivudine, and zidovudine. She became HIV-positive after her first OLT, developing graft failure 28 months later. She underwent retransplantion in May, 2001. Her HCV status remained undetectable for 1 year before repeat OLT and since retransplantation. Her HIV viral load is undetectable and the CD4 count greater than 400. Of the cases noted above from UM, none of the recipients have suffered from opportunistic infections, whereas two have developed HCV recurrence requiring pegylated interferon alfa 2b and ribavirin therapy.

Patient summaries: University of Pittsburgh Medical Center (UPMC)

The first case seen at the UPMC was a 43-year-old HIV-positive man with hemophilia suffering from HCV-related cirrhosis in September, 1997. His HIV viral load was undetectable, with a CD4 count of 660/mL at the time of OLT. He developed asymptomatic CMV viremia (pp65) and was treated with intravenous gancyclovir, then switched to oral gancyclovir. He was maintained on lamivudine, nelfinavir mesylate, and stavudine. He developed recurrent HCV on biopsy 21 months later and was treated with interferon alfa and ribavirin with normalization of his liver function tests. His HIV viral load has remained undetectable with a CD cell count of 280.

The second HIV-positive OLT recipient was a 48-year-old man with chronic HCV-related cirrhosis in December, 1998. He had an unremarkable post-OLT course except for recurrent HCV and was started on interferon alfa 2b and ribavirin on the sixth post-transplant month. He has received combination therapy, interferon alfa 2b, and ribavirin, and his HCV RNA converted to negative by 6 months and remains serologically negative for HCV while off antiviral therapy. His HAART regimen consists of lamivudine, nelfinavir mesylate, and stavudine and his most recent CD4 cell count is 199.

The third OLT recipient was a 43-year-old HIV-positive man with hemophilia suffering from HCV-related cirrhosis and was status 2A (ventilator and hemodialysis) at the time of transplantation. He was not on HAART at the time of OLT (January, 1999) because of liver failure, with an HIV viral load of 16,000/mL. Postoperatively, he developed ACR that required muromonab-CD3 therapy and progressed to sepsis with multiorgan system failure, dying 12 days after OLT.

The fourth case was a 44-year-old HIV-positive man with hemophilia and chronic HCV-related cirrhosis who underwent OLT in March, 1999. His HAART regimen consisted of Nelfinavir mesylate and lamivudine and zidovudine and his HIV viral load remained undetectable after the first year. The local physician discontinued the Nelfinavir mesylate without adjustment in his tacrolimus dose. He subsequently developed ACR, progressing on to chronic rejection. Treatment for rejection was complicated by HCV recurrence. He developed renal failure, requiring dialysis, and died 19 months after OLT.

The fifth HIV-positive OLT recipient was a 43-year-old woman suffering from HAART regimen drug hepatotoxicity and presenting with FHF. She underwent OLT in May, 2000. Her post-operative course was complicated by ACR that was treated with steroids and sirolimus therapy. She also experienced hepatic artery stenosis, which was treated by surgical reconstruction. The HAART regimen consisted of lamivudine and zidovudine and nelfinavir mesylate, and her HIV viral load is currently undetectable, with a CD4 cell count of 311.

The sixth OLT case was a 54-year-old HIV-positive man with cirrhosis secondary to chronic HCV who was transplanted in October, 2000. His post-operative course has been unremarkable. The HAART regimen consists of lamivudine, indinavir sulfate, and zalcitabine, with HIV viral load undetectable and a 1- year CD4 count of 328. His HCV is detectable at low levels, but he has no evidence of hepatitis on biopsy and is not on anti-HCV treatment.

The seventh case at UPMC was a 35-year-old HIV-positive man suffering from hemophilia, chronic HCV, and cirrhosis. Post-operatively he became CMV-viremic, although asymptomatic, and was treated with intravenous gancyclovir for 5 weeks and converted to oral cytovene therapy. His postoperative course has been unremarkable. The HAART regimen consists of lamivudine and zidovudine and nelfinavir mesylate, maintaining an undetectable HIV viral load and a CD4 count of 396. He has normal liver function tests without clinical HCV recurrence.

The eighth HIV-positive OLT recipient was a 50-year-old man suffering from chronic HCV with cirrhosis who underwent transplantation in October, 2001. He developed an asymptomatic CMV reactivation, requiring intravenous gancyclovir with conversion to oral cytovene. His HAART regimen consists of lamivudine and zidovudine and amprenavir, and his HIV viral load remains undetectable.

He developed mild HCV recurrence and is undergoing treatment with pegylated interferon and ribivirin with normal liver function tests.

The ninth case of HIV-positive OLT was performed for a 55-year-old man suffering from ESLD secondary to chronic HBV and hepatocellular carcinoma (HCC); he underwent transplantation in November, 2001. His post-operative course has been complicated by HCC recurrence; however, his HIV remains undetectable on a HAART regimen consisting of lamivudine, stavudine, and nelfinavir mesylate. The HBV-DNA is currently nondetectable. His HBV maintenance therapy is with lamivudine and hepatitis B immune globulin (HBIG).

The tenth HIV-positive OLT at UPMC was for a 67-year-old man suffering from chronic HBV and cirrhosis. He had documented YMDD mutation to lamivudine but was suppressed on adefovir dipivoxil before OLT. He was not on antiretroviral medications before OLT, had a HIV viral load of 24,000 copies/mL and a CD4 count of 176. He was transplanted in December, 2001. His postoperative course has been unremarkable, and he is tolerating his HAART regimen of adefovir dipivoxil, lamivudine, and zidovudine and nelfinavir mesylate. He is currently maintained on HBIG and adefovir dipivoxil.

Two patients (cases 3 [UM] and 10 (UPMC]) with FHF were listed and transplanted as UNOS status 1, 1 patient with advanced liver failure requiring ventilator and dialysis support was listed as UNOS status 2A, and the remainder underwent transplantation as UNOS status 2B. The patient listed as a status 2A (UPMC case 3) did not improve with transplantation and died soon thereafter. Overall, 2 patients (cases 3 and 4 [UPMC]) have died, of sepsis and HCV recurrence with chronic rejection, respectively.

Drug interactions

Protease inhibitors (PI) have been associated with significant cytochrome P450 3A interference. Therefore, tacrolimus dosing was reduced markedly to minimize levels of tacrolimus and resultant toxicity. For example, the average dose of tacrolimus was 1 to 3 mg/wk in HIV-positive OLT patients on PI. This contrasts with OLT patients not on PI, for whom dosing is approximately 0.1 mg/kg/d (7 mg/d). In one case in particular (case 9), the local physician discontinued the patient's PI without consulting the OLT team. The elimination of the PI from the HAART regimen resulted in a drastic reduction in tacrolimus levels, precipitating acute rejection. In another case, PI was started without adjustment in the tacrolimus, resulting in toxic levels (greater than 30 ng/mL) for 3 weeks. ACR developed in 4 of 13 patients (31%) in the early post-OLT period. All rejections in this period were controlled and easily reversed. The incidence of acute rejection was similar to that seen in the non-HIV OLT patients.

Post-operative care and HIV status

In all survivors, OLT reversed the symptoms of acute and chronic liver failure, including ascites, encephalopathy, muscle wasting, fatigue, hypersplenism and jaundice. One patient, case 2 (UM), developed lamivudine resistance, requiring additional treatment. Several recipients suffered from ACR, requiring steroid therapy, two of which necessitated muromonab (CD3) cluster therapy.

HIV loads remained undetectable in all but 1 patient during the entire follow-up period, and all are maintained on HAART therapy. Adjustments in the HAART regimen resulted in undetectable viral loads at follow up in the patient with recurrent HIV viremia. Total CD4 counts, which were all < 200 cells/mm3 before OLT, improved to > 200 cells/mm3 after OLT.

Survival and HCV recurrence

The 1-year survival in both groups of patients is 94% (15 of 16), 100% (6 of 6) at UM and 90% (9 of 10) at UPMC. One OLT recipient at UPMC died on day 570 as a result of noncompliance and resultant chronic rejection with recurrent HCV. Overall, HCV recurrence as diagnosed clinically and histologically occurred in 66% (2 of 3) of UM cases and 100% (7 of 7) of UPMC recipients. Assessment of long-term survival at 3 years or greater is not possible because of the small patient number; however, at 2 years, the actuarial survival is 80%, well within the expected survival for non-HIV-positive OLT patients according to UNOS statistics.

Author's discussion

Overall, there are an estimated 300,000 HIV persons co-infected with viral hepatitis B or C, or both, in the United States, representing a significant proportion of persons with HIV infection. With the advent of HAART, a decline in morbidity and mortality in patients with HIV infection have been observed over the past few years. As a result of this new treatment, mortality attributable to other underlying diseases such as viral hepatitis infection has increased, resulting in an increased prevalence of HIV patients with ESLD.

OLT is now an accepted therapy for a wide variety of irreversible diseases of the liver. At present, more than 4,000 liver transplantations are performed in the United States each year. Chronic HCV is the leading reason within the United States for OLT. Patients with HIV infection generally have been excluded from solid-organ transplantation. Because solid-organ transplantation is not considered for this subset of patients, death related to ESLD is imminent. The primary concern is the potential side effects of immunosuppression after OLT and the effect it may have on HIV disease progression. The conceptual conflict lies in the iatrogenic

immunosuppression of an already immunosuppressed individual (i.e., an HIV-positive patient). Early reports, before the advent of HAART, suggested that the course of HIV infection is accelerated in transplant patients, either because of the effect of immunosuppression on, or the role of alloantigenic stimulation in, HIV replication.

The exact role of immunosuppression in patients with HIV is unknown. However, the existence of HIV replication pathways that are inhibited by cyclosporine and tacrolimus have led some to consider employing these agents in the treatment of HIV infection. The early studies involving patients with HIV included cyclosporine as the primary immunosuppressant. Others have shown that mycophenolate mofetil, an inhibitor of the purine metabolism pathway, also potentiates some antiretroviral nucleoside analogs.

The first series of HIV patients that received OLT were HIV-positive at the time of transplantation or acquired the virus perioperatively was reported on by UPMC. This report predated the HAART era and, for most of its patients, even predated the availability of lamivudine monotherapy. In a retrospective serologic survey of organ donors and transplant recipients, seven of the 18 HIV-positive transplant recipients had antibodies to HIV before transplantation, whereas the other 11 HIV-positive recipients seroconverted at a mean of 96 days after transplantation. Nine of the 18 HIV-positive seropositive transplant recipients died a mean of 6 months after transplant surgery, and 9 (50%) were still alive a mean of 43 months after transplantation. Of the 15 liver transplant patients, 7 were alive at a mean of 2.75 years. This study did not show any survival statistical difference between the HIV-positive and negative patients. Although the HIV-positive patients did experience an increase in infectious complications, particularly those patients that required anti-lymphocyte antibody preparations during cyclosporine therapy. Similarly, when transplant patients with HIV and without HIV were compared, there was no statistical significance (P = .69) in regard to AIDS-free survival. Furthermore, HAART therapy was not available at that time; hence, there was no immune reconstitution in patients on therapy for HIV. In more recent follow-up (12.75 years), 2 liver transplant patients remained alive, both on anti-HIV therapy, instituted late after their OLT.

The European experience comes primarily from the King's College review of 5 patients, 3 transplants for chronic HCV cirrhosis. The rapid progression of HCV was a major concern because survival in this group of patients was between 6 and 25 months. In abstract form at the Eighth Conference on Retroviruses and Opportunistic Infections in 2001, the King's group reported on 7 co-infected patients, 4 with HCV recurrence, and an overall survival between 3 and 25 months. There are other European reports of transplantation in co-infected patients; however, they tend to predate the HAART regimen era.

It is important to recognize that not all patients with HIV and liver failure may be acceptable candidates for OLT. Patients with profound immunosuppression attributable to advanced AIDS or with a detectable viral load caused by HAART therapy from multiple drug resistance may not be good candidates for transplantation at this time. In addition, patients with advanced liver failure requiring life support such as dialysis or mechanical ventilation are high-risk candidates regardless of their HIV status. Of the 16 patients who underwent transplantation in this study, 2 died. One patient's death was related to sepsis from vancomycin-resistant enterococcal infection, unrelated to HIV, whereas the second patient's death was caused by chronic rejection and HCV recurrence. Overall, the 92% 1-year survival in this group of HAART regimen-treated HIV-positive patients is at least equal to that seen in the HIV-negative OLT patients.

HCV universally reoccurs after transplant and results in cirrhosis in over 20% of cases within 5 years, regardless of HIV status. However, the exact time and percentage of HCV recurrence can be debated. Recurrence and disease progression resulting in allograft injury as reported was a major concern in the King's College group. Patient survival in this subset was decreased as a result of HCV recurrence. The HCV-positive OLT recipients in our report had a better survival rate than those in the King's group. In fact, 1 UPMC recipient is alive at more than 5 years, and 1 recipient at UM is currently without HCV recurrence at more than 20 months after OLT. However, the impact of HIV and HCV recurrence and disease progression in OLT recipients in this small subset with relatively short follow-up does not allow us to draw a definitive conclusion. The development of HBV resistance to lamivudine occurred in only 1 patient at UM. Tenofovir was combined with the lamivudine, and the patient became HNB DNA-negative 6 months later.

We have performed 16 liver transplantations in patients with ESLD and HIV. The results have been encouraging, with excellent patient survival. During the period that our patients received HAART therapy, nearly all maintained adequate CD4 counts greater than 200 cells/mm3 and undetectable or low HIV viral loads. Our results suggest that patients with HIV suffering from ESLD can benefit from and survive OLT.

This experience suggests that OLT is effective in selected HIV-positive patients. We propose that while further follow-up of these patients to assess long-term benefits and risks is needed, more liberal application of OLT in selected HIV candidates be considered. Nationally, most centers continue to exclude the HIV population from OLT as a possible life-saving measure without sufficient objective information to support these practices. Without an OLT, patients with HIV and significant liver disease will not survive. In addition, we should consider HIV-positive patients who have extenuating circumstances, with detectable HIV viral loads before OLT when they may not be able to tolerate potent antiretroviral medications in the presence of significant liver dysfunction.

NATAP

National AIDS Treatment Advocacy Project
580 Broadway, Suite 1010
New York, NY 10012

Tel: 212-219-0106
Fax: 212-219-8473
Email: info@natap.org

www.natap.org